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Synthetic Methods |*Hot Paper*|

Direct Metal-Free Entry to Aminocyclobutenes or Aminocyclobutenols from Ynamides: Synthetic Applications

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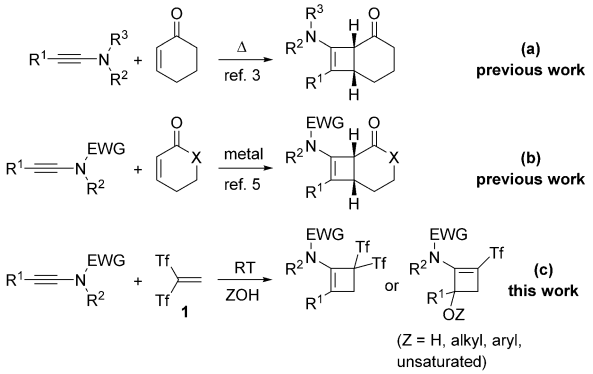
Abstract: The [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ has been developed to regioselectively afford bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with the ynamides bearing electron-rich aromatic rings at the C-terminal, an interesting reactivity switch was observed; a cyclization/hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. Aminocyclobutene construction with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3-(triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

Introduction

Functionalized cyclobutenes are important scaffolds present in several bioactive compounds, which have also been used as synthetic intermediates for the preparation of functionalized organic molecules.[1] Of particular interest is the aminocyclobutene structural motif.[2] A traditional method for aminocyclobutene preparation in a single step is the Ficini reaction, a [2+2] cycloaddition of ynamines with cyclic electron-deficient alkenes (Scheme 1 a).[3] However, the Ficini reaction presents a serious drawback, owing to the difficulty of preparing and handling reactive ynamines. More recently, ynamides,[4] which bear increased stability, has been proved as convenient substrates for the Ficini reaction (Scheme 1 b).[5] Unfortunately, their widespread use in aminocyclobutene synthesis is precluded by the narrow substrate scope of the alkene partner, which is normally a cyclic α,β-unsaturated carbonyl compound. An additional drawback is the use of environmentally unfriendly or expensive metallic salts, which are required for the activation of ynamides. Consequently, efficient metal-free synthesis of functionalized aminocyclobutenes with high chemo- and regioselectivity remains a challenge.



Scheme 1. [2+2] cycloadditions of ynamides with alkenes.

We contemplated a possible mild, metal-free synthesis of aminocyclobutenes through the reaction of the highly polarized reagent 1,1-bis(trifluoromethylsulfonyl)ethene (**1**)[6] with ynamides (Scheme 1 c). Of practical interest, 2-(2-fluoropyridinium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** was identified as a stable precursor of **1** with the transference of the Tf_2CCH_2 group to phenols, alkynes, 1,3-dienes, and azides.[7] Herein we describe the discovery and development of the uncatalyzed [2+2] cycloaddition of ynamides with $Tf_2C{=}CH_2$ **1** under mild conditions. Incidentally, with ynamides bearing electron-rich aromatic rings at the C-terminal, we observed an interesting reactivity switch.

Results and Discussion

Figure 1 and Figure 2 show the structures of starting ynamides **3a–j** and **3k–z′**, respectively. Initially we treated the oxazolidi-

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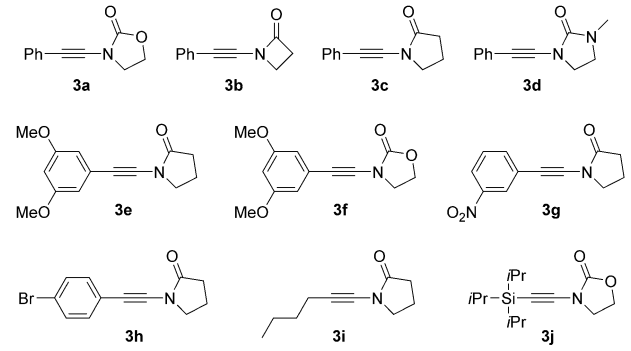


Figure 1. Structures of starting ynamides **3a–j**.

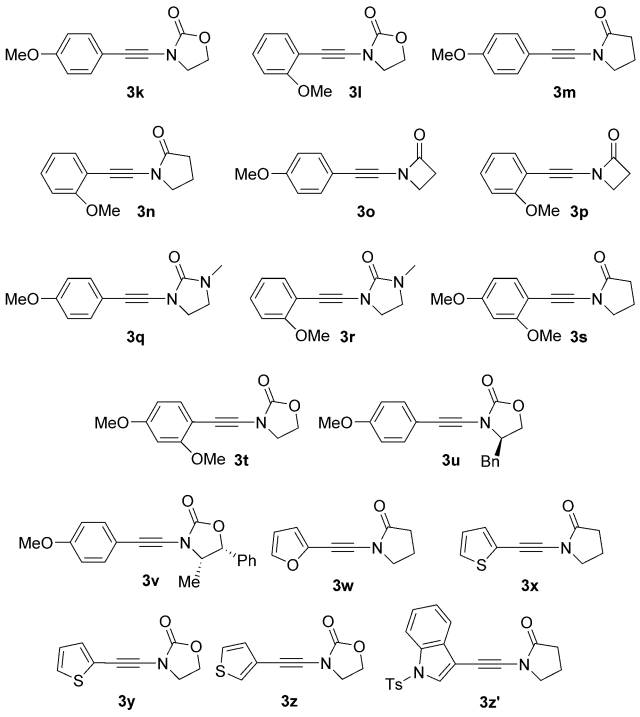
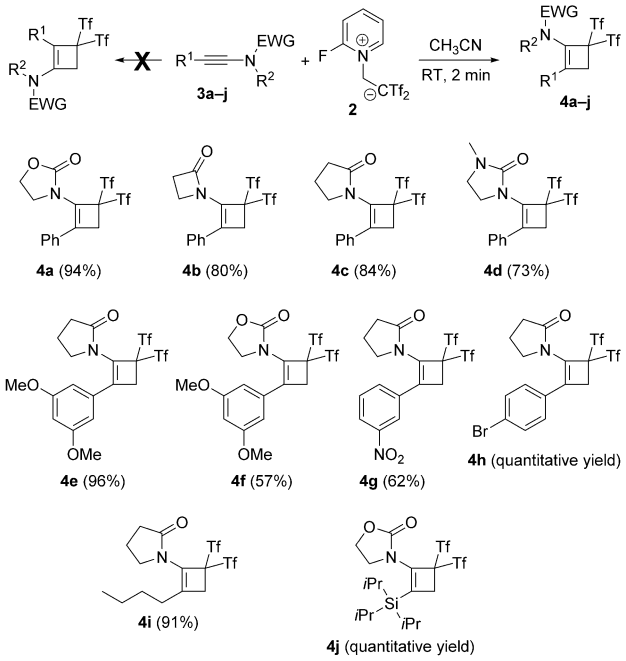


Figure 2. Structures of starting ynamides **3k–z′**.

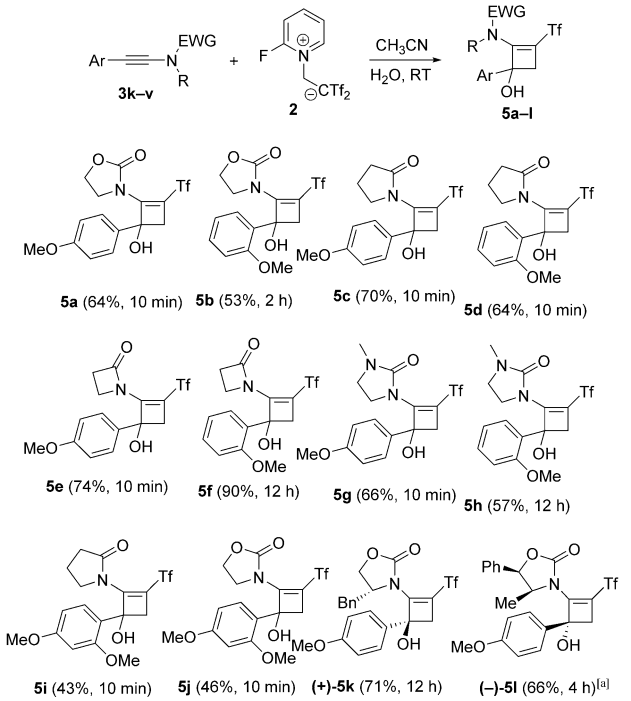
none-based phenyl ynamide **3a** with zwitterion **2** in acetonitrile at room temperature (the optimal conditions identified earlier in our laboratory for the reaction of pyridinium salt **2**).[7c,d] The nitrogenated functionality of ynamides can either become part of a possible five-membered azaheterocycle or be introduced as an amino substituent onto the required cyclobutene. Happily, the desired 4,4-bis(trifluoromethylsulfonyl)-cyclobut-1-enamide **4a** was cleanly formed with total regioselectivity and isolated in an excellent 94% yield (Scheme 2). It is important to note that excess of pyridinium salt **2** was not required and the use of equimolecular amounts of zwitterion was enough, thus not generating additional waste. Next, we decide to evaluate the generality of the reaction with respect to nitrogen functionalization. Azetidin-2-one-, pyrrolidin-2-one-, and imidazolidin-2-one-based phenyl ynamides **3b–d** were selected as the substrates to test our cyclization reaction. We



Scheme 2. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **4**.

were pleased to find that the desired four-membered carbocyclic products **4b–d** were smoothly obtained (Scheme 2). We then turned to examine a series of ynamides by varying substitution on the C-terminal. Thus, dimethoxyphenyl, nitrophenyl, and bromophenyl ynamides **3e–h** afforded adducts **4e–h** in 57%-quantitative yields (Scheme 2). The process was not limited to aromatic ynamides; alkyl-substituted ynamide **3i** also performed well to produce the expected product **4i**. Likewise, the silyl-protected acetylene **3j** survived the reaction very well to form **4j** in quantitative yield (Scheme 2). Ynamides that contained substituents with different electronic features were well-tolerated; with the present method becoming a facile route to aminocyclobutene scaffolds. Notably, ynamides **3a–j** instantaneously reacted to selectively give the corresponding aminocyclobutenes **4a–j**.[8]

Next, the general scope of the reaction with ynamides that contained electron-donating methoxy groups at the *ortho* or *para* positions of the benzene ring was examined. When electron-rich ynamides **3k–v** were subjected to the above conditions used for ynamides **3a–j**, a remarkable effect of the electronic properties of the starting alkyne on the product formation was observed. There was no evidence of the presence of type **4** products, with compounds **4k–v** probably undergoing further reaction. To our delight, acetylene derivatives **3k–y** underwent an appealing cyclization/hydroxylation sequence, yielding novel 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5a–j** (Scheme 3). A gram-scale synthesis of **5f** demonstrated the robustness of this methodology. Complete conversion was observed by thin-layer chromatography (TLC) and ^{1}H NMR spectroscopy of the crude reaction mixtures in all cases. However, side reactions were detected on highly activated ynamides **3s** and **3t**, which may be responsible for the



Scheme 3. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 1-aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5**. [a] Major isomer is shown (d.r. = 80:20).

moderate yields of isolated adducts **5i** and **5j**. To test the importance of the steric effects, enantiopure chiral ynamides **3u** and **3v** were prepared and tested. Despite the steric hindrance from the oxazolidinone substituents, aminocyclobutenols **5k** and **5l** were obtained in reasonable yields (Scheme 3). Adduct **5k** was obtained as single enantiomer, whereas adduct **5l** was obtained as an 80:20 diastereomeric mixture. For conclusive assessment of the structure of compounds **5**, an X-ray crystallographic analysis of adduct **5a** was undertaken (Figure 3).[9] On the basis of the structure of aminocyclobutenol **5a**, it must be assumed the participation of adventitious water. The addition of external water was not required, but the inclusion of 1.5 equivalents of H_2O accelerated the process. In view of the fact that all reported methods for accessing cyclobutenols

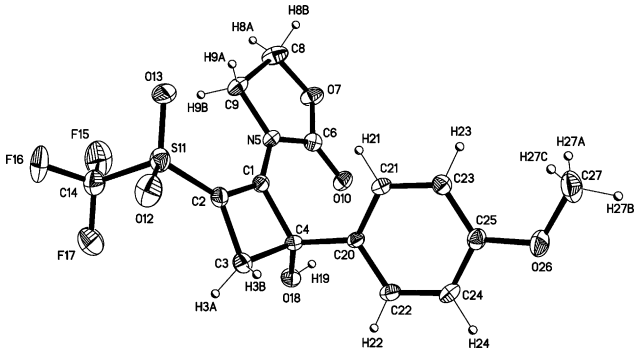
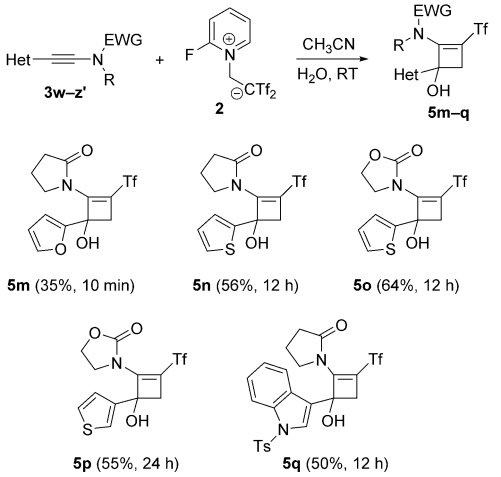


Figure 3. ORTEP representation of 2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol (**5a**). Thermal ellipsoids are shown at 50% probability.

should start from cyclobutenones, our protocol could open new horizons for the generation of cyclobutenols in a complementary selective manner by another mechanistically different strategy.

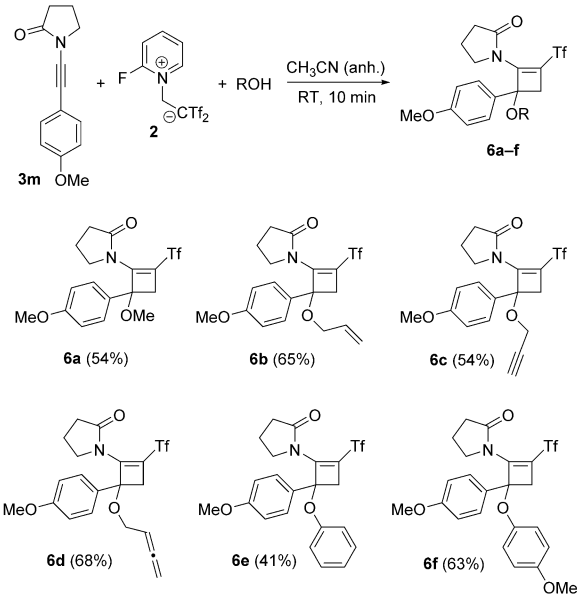
With a number of aromatic-substituted ynamides found to be compatible with the optimized reaction conditions, heteroaromatic rings were investigated to further expand the scope of the reaction (Scheme 4). Ynamides bearing at the C-terminal



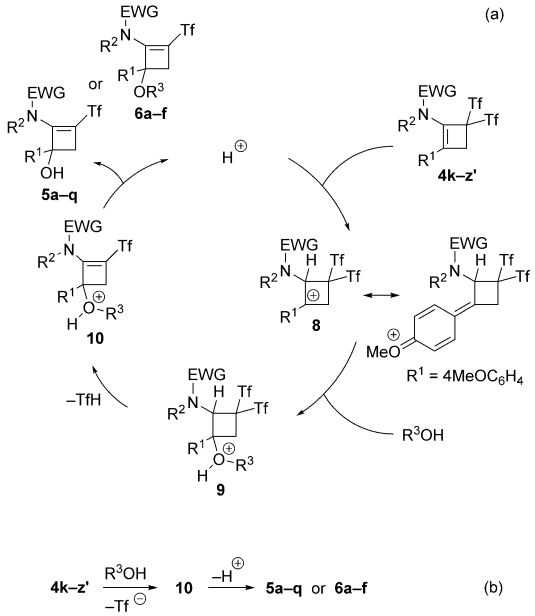
Scheme 4. Uncatalyzed reaction of ynamides **3** with zwitterion **2**. Controlled synthesis of 1-hetaryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols **5**.

several heterocycles including furan, thiophene, and indole did not reduce reactivity of the alkyne. Thus, ynamides **3w–z′** reacted with zwitterion **2** in acetonitrile at room temperature to give aminocyclobutenols **5m–q**. Again, it seems that moderately electron-rich rings have a better performance than highly activated ones (adduct **5m**). Substrate **3z′**, with a large group flanking the ynamide, smoothly underwent the desired transformation. Electronic but not steric variation of the ynamide derivatives played a role in determining the reactivity of alkynes **3**. The absence of hydroxylated products formed from ynamides **3a–j** points to a strong activating effect of electron-donating substituents in ynamides **3k–z′**.

Since the ratio products **4** and **5** may be considered an approximate measure of the relative reactivity of the aminocyclobutene ring towards oxygenated nucleophiles, we decided to perform the reaction of ynamide **3m** with alcohols under otherwise identical conditions. The studies of aminocyclobutene formation with addition of methanol, prop-2-en-1-ol, prop-2-yn-1-ol, and propa-1,2-dien-1-ol demonstrated that the presence of the alcohol moiety exlusively gives aminocyclobutenyl ethers **6a–d**, with the hydroxy group acting as a nucleophile (Scheme 5). Considering the versatility of alkenes, alkynes, and allenes in chemical transformations, cyclobutenes **6b–d** are potentially interesting building blocks for further manipulation. Despite the poor nucleophilicity of phenols, they exhibit ambident reactivity because phenols bear two reaction sites, namely O and C.[10] With regards to selectivity, a major challenge with the use of phenols is to obtain exclusively aryloxyla-



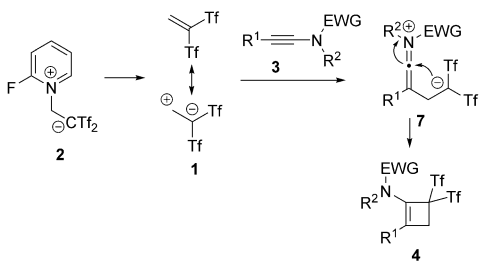
Scheme 5. Uncatalyzed reaction of ynamide **3m** with zwitterion **2** in presence of alcohols. Controlled synthesis of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones **6**.



Scheme 7. Mechanistic explanation for the synthesis of aminocyclobutenes **5** and **6**.

tion or hydroarylation products. Interestingly, the use of phenol and mequinol resulted in the sole formation of the corresponding phenoxy derivatives **6e** and **6f** (Scheme 5). However, the formation in 10% yield of cyclobutenol **5c** together with adduct **6e** revealed that water addition is a competitive reaction in the case of phenol but not for mequinol. It should be noted that aminocyclobutenyl ethers **6a–f** could be isolated and characterized, but they are not as stable as related aminocyclobutenols **5a–l**. The higher stability of cyclobutenols may be ascribed to hydrogen bonding, as indicated by an intramolecular O10···H19 contact in the X-ray diffraction analysis of compound **5a**.

Proposed mechanisms for the formation of aminocyclobutenes **4–6** from 2-(2-fluoropyridinium-1-yl)-1,1-bis(trifluoromethylsulfonyl)ethan-1-ide **2** and ynamides **3** are shown in Schemes 6 and 7. It may initially involve the formation of alkene **1**, which may be considered as a resonance hybrid between dipolar and uncharged species, from zwitterion **2**. Next, the stepwise [2+2] cycloaddition reaction between ynamides **3** and the in situ-generated bis(trifluoromethylsulfonyl)ethene



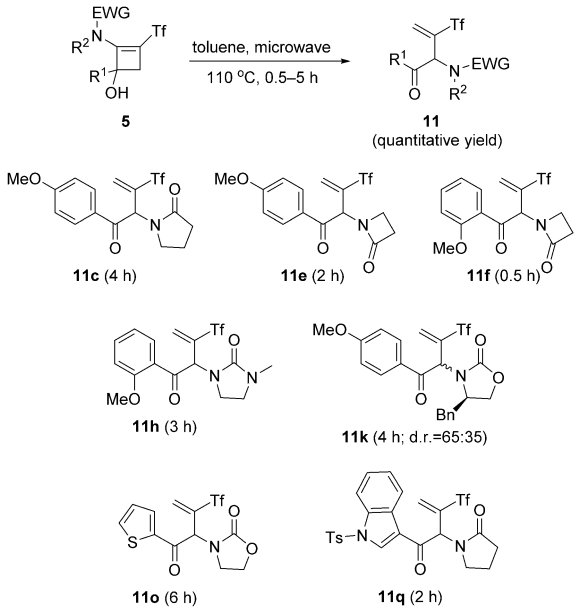
Scheme 6. Mechanistic explanation for the synthesis of aminocyclobutenes **4** from ynamides **3** and zwitterion **2**.

1 should take place, initially leading to the zwitterionic species **7**. The addition product **7** initiates a ring-closing reaction to afford 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides **4**. The observed exquisite regiocontrol may arise from the stabilization imparted by the amide group in intermediate **7**, which overrides the effect of the other substituent. For activated ynamides **3k–z′**, the presence of water or alcohols in the reaction media could trigger a rapid nucleophilic attack with concomitant trifluoro(hydrosulfonyl)methane (TfH) elimination, thus leading to the final 1-aryl-2-amino-3-(trifluoromethylsulfonyl)-cyclobut-2-enols **5** or 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones **6**. The conversion of aminocyclobutenes of type **4** into adducts **5** and **6** could be catalyzed by protons (Scheme 7a, top side). A possible pathway for the formation of adducts **5** and **6** may initially involve the formation of carbocations **8** through addition of the proton to the enamine double bond in transient 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamide intermediates **4k–z′**. The driving force of this process may be related to the stabilization of the positive charge in intermediates **8** by electron-rich substituents. Next, intermolecular nucleophilic attack of the oxygen at the benzylic position of cationic species **8** would form an oxonium cation of type **9**. Subsequent loss of TfH-generated species **10** followed by proton release afforded aminocyclobutenol derivatives **5** and **6** with concurrent regeneration of the catalyst.

The treatment of cyclobut-1-enamide **4c** with water under acidic catalysis (HCl, H_2SO_4 or TfOH) did result in complex reaction mixtures. This experimental result, combined with the unusual protonation of enamides at the α-carbon, led us to propose an alternative mechanism for the formation of cyclobutenol derivatives **5** and **6** (Scheme 7b, bottom side). In this way, the direct nucleophilic attack of water or alcohols into the ben-

zylic position should produce intermediate **10** with concomitant Tf^- release.

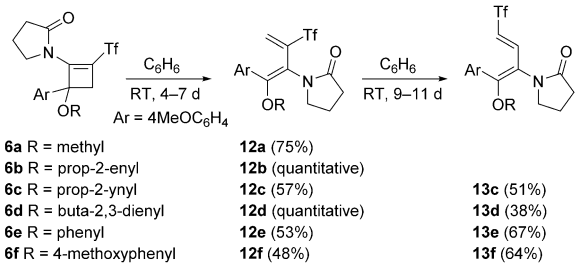
Having developed a direct approach to aminocyclobutenol derivatives **5a–q** and **6a–f** as single isomers from ynamides, we were then interested in using the inherent ring strain[11] of these highly functionalized four-membered carbocycles to perform a selective carbon–carbon bond fragmentation as a new entry to aminoalkenes. Attempts to generate a ring-opened structure from **5c** in refluxing benzene failed. Ring opening of substrate **5c** was successfully accomplished in a microwave reactor by heating a solution of aminocyclobutenol **5c** in toluene at 110 °C (Scheme 8). In this way, α-amino-β,γ-unsaturated



Scheme 8. Ring opening of aminocyclobutenols **5**. Synthesis of 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **11**.

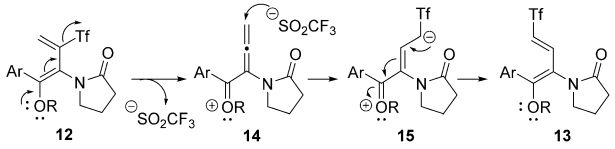
ketone **11c** was cleanly obtained in quantitative yield. Remarkably, this rearrangement was the only operative reaction mode. Accordingly, we carried out the thermally promoted ring opening of several adducts **5** and we smoothly obtained the corresponding 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones **11e**, **11f**, **11h**, **11k**, **11o**, and **11q** in quantitative yields. Enantioenriched oxazolidinone **11k** was formed as diasteromeric mixture (d.r. = 65:35) at the newly generated stereogenic center. In all these cases, we once again observed the sole formation of the β,γ-unsaturated ketone (Scheme 8). It should be noted that traditional strategies for the preparation of functionalized β,γ-unsaturated ketones are problematic owing to the possible isomerisation to the α,β-unsaturated ketone.

The utility of 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones as precursors for further elaboration is demonstrated in Scheme 9. When adduct **6a** was dissolved in benzene at room temperature, the 4π-electrocyclic ring opening to placeto give the (*Z*)-1-methoxy-1-aryl-3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amine derivative **12a** in



Scheme 9. Ring opening of alkoxycyclobutenamines **6**. Synthesis of functionalized buta-1,3-dien-2-amines **12** and **13**.

good yield. Similarly, the use of compounds **6b–f** as starting materials also efficiently promoted the fragmentation. In each case, (*Z*)-1,3-dienes **12a–f** were formed with total stereoselectivity.[12] The crude reaction mixtures are extremely clean for aminocyclobutenes **6b** and **6d**, giving dienes **12b** and **12d** as the only products detected. Remarkably, the mild conditions of the rearrangement allow the selective formation of diene **12d** without harming the sensitive allene functionality (Scheme 9). Surprisingly, 3-(trifluoromethylsulfonyl)buta-1,3-dien-2-amines **12** can undergo a further reaction in benzene solution through a spontaneous uncatalyzed migration process at room temperature to give (1*Z*,3*E*)-1-alkoxy-1-aryl-4-(trifluoromethylsulfonyl)-buta-1,3-dien-2-amines **13c–f** (Scheme 9). To explain the conversion of **12** into **13**, we must invoke the versatility of sulfone-type groups, which can act as both leaving groups and as nucleophiles.[13] Thus, the critical step in the formal triflyl migration of dienes **12** is the elimination of a trifluoromethanesulfinate anion to afford the allenamide intermediate **14** (Scheme 10). Next, nucleophilic addition of the trifluoromethanesulfinate anion to the terminal allene carbon of **14** generates zwitterionic species **15**, which, after a final rearrangement, produces triflones **13** (Scheme 10).



Scheme 10. Mechanistic explanation for the formal triflyl migration in dienes **12**.

Conclusions

In conclusion, the [2+2] cycloaddition of ynamides with the highly polarized reagent $Tf_2C{=}CH_2$ regioselectively afforded bis(triflyl)aminocyclobutenes in the absence of catalyst under mild conditions. Incidentally, with ynamides bearing electron-rich aromatic rings at the C-terminal, an interesting reactivity switch was observed. In such cases, a cyclization/hydroxylation sequence yielded 2-amino-3-(triflyl)cyclobut-2-enols. The study of aminocyclobutene formation with addition of alcohols resulted in the formation of aminocyclobutenyl ethers through a cyclization/hydroalkoxylation process. Moreover, the utility of

functionalized aminocyclobutenes as precursors for further elaboration was demonstrated with the preparation of α-amino-β,γ-unsaturated ketones and 3-(triflyl)buta-1,3-dien-2-amines through 4π-electrocyclic ring opening.

Experimental Section

General methods: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AVIII-700 with cryoprobe, Bruker AMX-500, Bruker Avance-300, or Varian VRX-300S. NMR spectra were recorded in $CDCl_3$ solutions, except otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H:, $\delta=0.0$ ppm), or $CDCl_3$ (^{1}H: $\delta=7.27$ ppm; ^{13}C: $\delta=76.9$ ppm), or [D$_6$]acetone (^{1}H: $\delta=2.0$ ppm; ^{13}C: $\delta=206.3$ ppm), or C_6D_6 (^{1}H: $\delta=7.16$ ppm; ^{13}C: $\delta=128.0$ ppm), or CD_3CN (^{1}H: $\delta=2.0$ ppm; ^{13}C: $\delta=118.2$ ppm). Low- and high-resolution mass spectra were taken on an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. IR spectra were recorded on a Bruker Tensor 27 spectrometer. X-Ray crystallographic data were collected on a Bruker Smart CCD difractomer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) operating at 50 Kv and 35 mA with an exposure of 30.18 s in ω. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

Synthetic procedures

General procedure for 4,4-bis(trifluoromethylsulfonyl)cyclobut-1-enamides 4a–j: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (1.0 mmol) was added at room temperature to a solution of the appropriate ynamide **3a–j** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until the starting material had disappeared (instantaneous reaction), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenes **4** follow.[14]

4,4-Bis(trifluoromethylsulfonyl)cyclobut-1-enamide 4a: From ynamide **3a** (30 mg, 0.16 mmol), flash chromatography of the residue using hexanes/ethyl acetate (9:1) as eluent gave compound **4a** (72 mg, 94%) as a colorless solid. M.p. 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.45$ (m, 5H, CH^{Ar}), 4.52 (dd, 2H, $J=8.7$, 7.1 Hz, CH_2), 4.07 (dd, 2H, $J=8.9$, 6.9 Hz, CH_2), 3.53 ppm (s, 2H, CH_2-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=154.0$ (C=O), 147.8 (C=*C*-N), 131.9 (CH^{Ar}), 129.1 (*C*=C-N), 128.9 (2CH^{Ar}), 128.4 (2CH^{Ar}), 119.8 (q, *J*(C,F) = 331.3 Hz, $2CF_3$), 117.9 (C^{Ar-q}), 88.4 (CTf_2), 63.1 (CH_2), 44.8 (CH_2), 31.8 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-69.87$ ppm (s, 6F, $2CF_3$); IR ($CHCl_3$): $\tilde{\nu}=1771$ (C=O), 1669 (C=C), 1380, 1104 (O=S=O), 1201 cm^{-1} (C–F); HRMS (ES): calcd for $C_{15}H_{11}NO_6S_2F_6$ $[M]^+$: 478.9932; found: 478.9928.

General procedure for 1-substituted-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enols 5a–q: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (1.0 mmol) and water (1.5 mmol) were sequentially added at room temperature to a solution of the appropriate ynamide **3k–z′** (1.0 mmol) in acetonitrile (10 mL). The reaction was stirred at room temperature until the starting material had disappeared (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenols **5** follow.

1-Aryl-2-amino-3-(trifluoromethylsulfonyl)cyclobut-2-enol 5a: From ynamide **3k** (50 mg, 0.23 mmol), flash chromatography of the residue using hexanes/ethyl acetate (97:3) as eluent gave compound **5a** (60 mg, 64%) as a colorless solid. M.p. 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta=7.32$ (m, 2H, 2CH^{Ar}), 6.91 (m, 2H, 2CH^{Ar}), 4.58 (m, 3H, CH_2, OH), 4.36 (m, 1H, CH*H*), 4.22 (m, 1H, C*H*H), 3.82 (s, 3H, OCH_3), 3.19 (d, 1H, $J=10.4$ Hz, CH*H*-*cyclobutene*), 2.88 ppm (d, 1H, $J=10.4$ Hz, C*H*H-*cyclobutene*); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): $\delta=159.4$ (C^{Ar-q}–OCH_3), 155.3 (C=O), 154.2 (C=*C*-N), 132.1 (C^{Ar-q}), 125.0 (2CH^{Ar}), 119.9 (q, *J*(C,F) = 325.6 Hz, CF_3), 114.2 (2CH^{Ar}), 101.1 (*C*=C-N), 77.8 (C^q-OH), 64.4 (CH_2), 55.2 (OCH_3), 45.4 (CH_2), 44.8 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): $\delta=-78.34$ ppm (s, 3F, CF_3); IR ($CHCl_3$): $\tilde{\nu}=3483$ (OH), 1770 (C=O), 1620 (C=C), 1398, 1127 (O=S=O), 1198 cm^{-1} (C–F); HRMS (ES): calcd for $C_{15}H_{14}NO_6SF_3$ $[M]^+$: 393.0494; found: 393.0478. X-ray data of **5a**: crystallized from ethyl acetate/*n*-hexane at 20 °C; $C_{15}H_{14}F_3NO_6S$ ($M_r=393.33$); orthorhombic; space group = *Pbca*; $a=8.8736(6)$, $b=19.2477(14)$, $c=39.638(3)$ Å; $\alpha=90$, $\beta=90$, $\gamma=90°$; $V=6770.1(8)$ Å^3; $Z=16$; cd = 1.544 mg m^{-3}; $\mu=0.256$ mm^{-1}; F(000) = 3232. 5974 ($R_{int}=0.0939$) independent reflections were collected on a Bruker Smart CCD difractomer using graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda=0.71073$ Å) operating at 50 kV and 35 mA. The structure was solved by direct methods and was refined by full-matrix least-squares procedures on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in calculated positions and refined riding on the respective carbon atoms. Final *R* indices [$I>2\sigma(I)$] values were *R*1 (reflns obsd) = 0.0513 (2529), *wR*2 (all data) = 0.1533.[9]

General procedure for 4-alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-ones 6a–f: 2-(2-Fluoropyridin-1-ium-1-yl)-1,1-bis[(trifluoromethyl)sulfonyl]ethan-1-ide **2** (0.1 mmol) and the corresponding alcohol or phenol (0.15 mmol) were sequentially added at room temperature to a solution of ynamide **3m** (0.1 mmol) in acetonitrile (1 mL). The reaction was stirred at room temperature until the starting material had disappeared (TLC), and then the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for aminocyclobutenyl ethers **6** follow.

4-Alkoxy-4-aryl-2-(trifluoromethylsulfonyl)cyclobut-1-enyl pyrrolidin-2-one 6d: From ynamide **3m** (30 mg, 0.139 mmol), flash chromatography of the residue using hexanes/ethyl acetate (95:5→9:1) as eluent gave compound **6d** (42 mg, 68%) as a colorless oil. ^{1}H NMR (300 MHz, C_6D_6, 25 °C): $\delta=7.61$ (m, 2H, 2CH^{Ar}), 6.79 (m, 2H, 2CH^{Ar}), 5.34 (m, 1H, *CH*=·=CH_2), 4.65 (m, 2H, CH=·=*C*H_2), 4.11 (m, 1H, OCH*H*), 3.97 (m, 1H, OC*H*H), 3.38 (m, 2H, CH_2), 3.28 (m, 4H, OCH_3, CH*H*-*cyclobutene*), 2.95 (d, 1H, $J=11.2$ Hz, C*H*H-*cyclobutene*), 1.38 (m, 2H, CH_2), 0.87 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): $\delta=209.2$ (C=*C*=C), 172.3 (C=O), 159.8 (C^{Ar-q}–OCH_3), 156.1 (C=*C*-N), 130.6 (C^{Ar-q}), 126.8 (2CH^{Ar}), 120.9 (q, *J*(C,F) = 326.9 Hz, CF_3), 114.1 (2CH^{Ar}), 100.5 (*C*=C-N), 88.6 (*CH*=C=CH_2), 83.4 (C^{Cq}-OCH_2CH=C=CH_2), 76.3 (CH=C=*C*H_2), 63.5 (OCH_2), 54.8 (OCH_3), 48.0 (CH_2), 42.2 (CH_2), 29.6 (CH_2), 18.0 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): $\delta=-77.64$ ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}=1958$ (C=C=C), 1761 (C=O), 1596 (C=C), 1365, 1112 (O=S=O), 1208 (C–O), 1185 cm^{-1} (C–F); HRMS (ES): calcd for $C_{20}H_{20}NO_5SF_3$ $[M]^+$: 443.1014; found: 443.1016.

General procedure for 2-amino-3-(trifluoromethylsulfonyl)but-3-en-1-ones 11: A stirred solution of the appropriate aminocyclobutenol **5** (0.1 mmol) in toluene (2.0 mL) was heated at 110 °C under

microwave irradiation until the starting material had disappeared (TLC). The reaction was allowed to cool to room temperature and concentrated under vacuum. Further purification was not necessary. Spectroscopic and analytical data for pure forms of compound **11 c** follow.

2-Amino-3-(trifluoromethylsulfonyl)but-3-en-1-one 11 c: From aminocyclobutenol **5 c** (36 mg, 0.09 mmol), compound **11 c** (36 mg, quantitative yield) was obtained as a green pale oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.99 (m, 2H, 2CH^{Ar}), 6.97 (m, 2H, 2CH^{Ar}), 6.95 (d, 1H, J = 1.9 Hz = CH*H*), 6.75 (s, 1H, CH-N), 6.55 (s, 1H, =C*H*H), 3.89 (s, 3H, OCH_3), 3.60 (m, 1H, CH*H*), 3.35 (m, 1H, C*H*H), 2.45 (m, 2H, CH_2), 2.07 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 191.1 (C=O), 175.9 (NC=O), 164.7 (C^{Ar-q}–OCH_3), 140.1 (=CH_2), 139.2 (=*C*-Tf), 131.3 (2CH^{Ar}), 126.5 (C^{Ar-q}), 119.6 (q, J(C,F) = 327.1 Hz, CF_3), 114.4 (2CH^{Ar}), 55.6 (OCH_3), 53.7 (CH-N), 44.8 (CH_2), 30.5 (CH_2), 18.4 ppm (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −77.41 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1690 (NC=O, C=O), 1601 (C=C), 1366, 1104 (O=S=O), 1213 cm^{-1} (C–F); HRMS (ES): calcd for $C_{16}H_{16}NO_5SF_3$ $[M]^+$: 391.0701; found: 391.0698.

General procedure for the synthesis of buta-1,3-dien-2-amines 12: A solution of the appropriate alkoxycyclobutenamine **6** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until the starting material had disappeared (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **12** follow.

Buta-1,3-dien-2-amine 12 a: From aminocyclobutenyl ether **6 a** (20 mg, 0.049 mmol), flash chromatography of the residue using hexanes/ethyl acetate (8:2) as eluent gave compound **12 a** (15 mg, 75%) as a bright yellow oil. ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ = 7.08 (m, 2H, 2CH^{Ar}), 6.56 (m, 2H, 2CH^{Ar}), 6.27 (s, 1H, =CH*H*), 6.08 (s, 1H, =C*H*H), 3.59 (t, 2H, J = 7.1 Hz, CH_2), 3.14 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 2.08 (t, 2H, J = 8.1 Hz, CH_2), 1.56 ppm (m, 2H, CH_2); ^{13}C NMR (125 MHz, C_6D_6, 25 °C): δ = 175.0 (C=O), 161.0 (C^{Ar-q}–OCH_3), 159.1 (C=*C*-N), 142.0 (=CH_2), 140.7 (*C*=C-N), 131.5 (2CH^{Ar}), 123.3 (C^{Ar-q}), 120.5 (q, J(C,F) = 327.8 Hz, CF_3), 114.3 (2CH^{Ar}), 112.0 (=*C*-Tf), 56.8 (OCH_3), 54.7 (OCH_3), 48.0 (CH_2), 30.6 (CH_2), 19.0 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −78.15 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1698 (C=O), 1606 (C=C), 1360, 1115 (O=S=O), 1209 cm^{-1} (C–F); HRMS (ES): calcd for $C_{17}H_{18}NO_5SF_3$ $[M]^+$: 405.0858; found: 405.0868.

General procedure for the synthesis of buta-1,3-dien-2-amines 13: A solution of the appropriate buta-1,3-dien-2-amine **12** (0.1 mmol) in benzene (0.1 mL) was stirred at room temperature until the starting material had disappeared (TLC). Then, the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel eluting with hexanes/ethyl acetate mixtures gave analytically pure compounds. Spectroscopic and analytical data for buta-1,3-dien-2-amines **13** follow.

Buta-1,3-dien-2-amine 13 e: From buta-1,3-dien-2-amine **12 e** (14 mg, 0.029 mmol), flash chromatography of the residue using hexanes/ethyl acetate (8:2→7:3) as eluent gave compound **13 e** (9.4 mg, 67%) as a bright yellow oil; ^{1}H NMR (300 MHz, C_6D_6, 25 °C): δ = 7.91 (d, 1H, J = 14.7 Hz, Tf–CH=C*H*), 7.13 (m, 2H, 2CH^{Ar}), 6.96 (m, 2H, 2CH^{Ar}), 6.87 (m, 2H, 2CH^{Ar}), 6.65 (m, 1H, CH^{Ar}), 6.42 (m, 2H, 2CH^{Ar}), 6.32 (d, 1H, J = 14.7 Hz, Tf–*CH*=CH), 2.95 (s, 5H, OCH_3, CH_2), 1.85 (t, 2H, J = 8.0 Hz, CH_2), 1.20 ppm (m, 2H, CH_2); ^{13}C NMR (75 MHz, C_6D_6, 25 °C): δ = 174.0 (C=O), 165.0 (C=*C*-N) 162.4 (C^{Ar-q}–OCH_3), 156.3 (C^{Ar-q}–O-C=), 150.0 (Tf–CH=CH), 132.9 (2CH^{Ar}), 129.7 (2CH^{Ar}), 124.3 (CH^{Ar}), 123.2 (C^{Ar-q}), 120.8 (q, J(C,F) = 324.7 Hz, CF_3), 119.6 (2CH^{Ar}), 119.2 (C=C-N), 114.4 (2CH^{Ar}), 113.5 (Tf–CH=CH), 54.7 (OCH_3), 46.8 (CH_2), 30.1 (CH_2), 18.9 ppm (CH_2); ^{19}F NMR (282 MHz, C_6D_6, 25 °C): δ = −78.12 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 1705 (C=O), 1580 (C=C), 1358, 1117 (O=S=O), 1205 cm^{-1} (C–F); HRMS (ES): calcd for $C_{22}H_{20}NO_5SF_3$ $[M]^+$: 467.1014; found: 467.1019.

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[14] Experimental procedures, as well as full spectroscopic and analytical data, for compounds not included in this Experimental Section are described in the Supporting Information. It contains compound characterization data, experimental procedures, and copies of NMR spectra for all new compounds.

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